CHAPTER VIII

CLINICAL USE OF ŒSTROGENS

Choice of Œstrogens. A large number of œstrogenic compounds have been studied both in experimental animals and in the human subject. It appears that the ratio of potency differs in the human species from what has been established in laboratory animals. Table 6 shows the relative potency of eight œstrogens

TABLE 6. *The Relative Activities of a Number of Œstrogens Compiled from studies on rats by W. A. Broom and on human beings by P. M. F. Bishop*

Œstrogen	Relative Activity		
	Rats		Human Oral
	Injection	Oral	
Stilbœstrol	100	100	100
Dienœstrol	28	68	25
Hexœstrol	75	10	6
7-methyl bisdehydrodoisynolic acid	46	500	20
Ethinyl œstradiol . . .	230	20	2000
Equine conjugated œstrogen .	8	5	50
Sodium stilbœstrol sulphate .	app. 12	50	40
Œstrone	30	2	7

as determined on the one hand by the rat vaginal smear method, and on the other by the production of withdrawal bleeding in amenorrhœic women. Using this end-point and comparing each of the other œstrogens with stilbœstrol, dienœstrol is roughly a quarter as potent, hexœstrol twenty times less potent, doisynolic acid one fifth as potent, ethinylœstradiol twenty times more potent, " equine conjugated œstrogen " half as potent, stilbœstrol sulphate less than half as potent and œstrone fifteen times less potent. Recent trials with equilin have shown it to be a third as potent. This ratio is roughly that of " equine conjugated œstrogen," which probably owes its œstrogenic potency to its content of equilin. Equilin is therefore about seven times more potent than œstrone, though in the animal experiments it has proved to be slightly less potent than œstrone. These human

comparisons apply of course only to one level of œstrogenic response, namely production of withdrawal bleeding in amenorrhœic women. It is possible that at lower levels of response, such as control of menopausal hot flushes, or higher levels, such as inhibition of lactation, other potency ratios may exist.

Three factors must be taken into consideration in the choice of an œstrogen for clinical use ; potency, cost and " toxicity." It is seldom necessary to administer œstrogen by injection as the oral activity of some of the available œstrogens is very high. Hexœstrol and œstrone are comparatively so weak that there is little indication for their use. Stilbœstrol is a satisfactorily potent œstrogen and ethinylœstradiol is an extremely effective compound. Equilin is the most potent completely " natural " œstrogen available for oral use. Stilbœstrol, dienœstrol and hexœstrol are relatively cheap, whereas natural œstrogens such as œstrone, equilin and equine conjugated œstrogens, and their derivatives such as ethinylœstradiol are relatively expensive. One needs, however, only a twenty-fifth of the amount of ethinylœstradiol as compared with stilbœstrol. There is no doubt that stilbœstrol is much more liable to produce nausea or vomiting than any of the other compounds. In fact, the therapeutic range and the " toxicity " range overlap considerably, so that it is frequently impossible to achieve a therapeutic result without inducing nausea or vomiting. Nevertheless if care is taken to determine the minimal effective dose the incidence of " toxicity " is considerably lower than is at the moment popularly believed. However, in many cases stilbœstrol has to be abandoned because of its " toxicity." Ethinylœstradiol is less toxic than stilbœstrol, though nausea and vomiting are commonly encountered in the higher, and even sometimes in the medium, dosage range. Dienœstrol is relatively cheap and only very slightly " toxic." The natural œstrogens are always considered to be non-toxic, though severe vomiting may be induced with very high doses, such as may be required for œstrogen hæmostasis. They are however expensive. Nevertheless equine conjugated œstrogen or equilin may prove valuable if it is necessary to give high doses which, if synthetic œstrogens were employed, would almost certainly induce severe vomiting. Menopausal women are most liable to complain of nausea and vomiting, non-pregnant women usually complain of nausea in high doses, pregnant and puerperal women will never show " toxic " side-effects, and men will seldom do so. This is presumably due to the manner in which œstrogens are metabolized in these various groups.

To sum up : Stilbœstrol is a cheap, potent and reliable œstrogen which gives consistent results, but rather frequently produces nausea or vomiting. Dienœstrol is also cheap but less liable to induce nausea. Ethinylœstradiol, though rather more expensive, is extremely potent and not by any means devoid of " toxicity " risks in high doses. Equilin is a potent natural œstrogen and seldom induces toxic effects. It is, however, not yet on the market. Equine conjugated œstrogen is an extract of pregnant mare urine promptly frozen on voiding, and probably owes its œstrogenic activity to equilin. It is distributed in Canada and the United States under the trade name of " Premarin." It is highly potent, rather expensive, and for practical purposes non-toxic, but it is not available at the moment in this country. In certain circumstances, therefore, œstradiol benzoate by injection may be required in order to achieve sufficient concentration if high doses have to be administered.

Dosage. The following dosage schedules cover the various therapeutic indications :

Low Dosage. 0·1–1 mgm. of stilbœstrol daily (or its equivalent where other œstrogens are employed). This represents the dose which will control menopausal symptoms, such as hot flushes.

Moderate Dosage. 1–3 mgm. of stilbœstrol daily (or its equivalent). This is used in some gynæcological disorders, and in certain skin diseases.

High Dosage. 5–15 mgm. (or more) of stilbœstrol daily (or its equivalent). This is used for œstrogen hæmostasis, inhibition of lactation, and carcinoma of the breast and prostate.

Pregnancy Dosage. Up to 135 mgm. of stilbœstrol daily have been advocated for the treatment of pregnancy disorders such as toxæmia, pre-eclampsia and diabetes.

Therapeutic Indications

At the Menopause. At the time when ovarian function is gradually failing œstrogen replacement therapy is singularly effective, provided that care is taken to moderate the dose. Low doses are not only adequate but imperative, for over-dosage raises the threshold of resistance to subsequent œstrogenic administration. It is therefore important to find the lowest possible daily dose of œstrogen which will control the hot flushes and other manifestations of the menopause. This dose is usually between 0·1 and 1 mgm. of stilbœstrol (or its equivalent), and usually averages 0·3 to 0·5 mgm. a day. Higher doses often

give rise to bloated feelings, headaches and a recurrence of hot flushes (the " escape " effect). Treatment, even with these very small doses, may give rise to uterine bleeding if continued indefinitely, and it is often advisable to give the daily dose for three to six weeks continuously and then stop for a week to allow a scanty withdrawal bleeding to take place. It is not, of course, suggested that œstrogen therapy alone will control the extremely complex menopausal syndrome. Sympathy and reassurance are essential and it is important that adequate treatment of insomnia should also accompany the specific endocrine therapy.

In Gynæcology. *Amenorrhœa* is often associated with inadequate œstrogen secretion in cases of " menstrual instability " in which the menstrual cycles become gradually prolonged and may eventually cease altogether. Sudden amenorrhœa, on the other hand, following normal regular periodicity is often due to hypothalamic inhibition and therefore seldom yields to endocrine therapy. " Œstrogen withdrawal bleedings " can usually be induced if œstrogens are administered in fortnightly courses. In almost every case of hypothalamic amenorrhœa such treatment does not lead to restoration of normal menstrual rhythm. In about 25 per cent. of cases of menstrual instability, normal cycles will be restored, if care is taken to find the dose which will just induce withdrawal bleeding, though subsequent relapses are not infrequent. An interval of at least a week is allowed to elapse between successive courses. It is reasonable to give this treatment a trial in cases of infertility due to amenorrhœa and failure to ovulate. In some infertile women, post-coital tests are persistently negative during the ovulatory phase of the menstrual cycle. This may be due to scanty cervical secretion with consequent absence of sperms. Small doses of œstrogen, such as 0·25 to 0·5 mgm. stilbœstrol, may improve the quality and quantity of the *cervical fluid.* Larger doses may delay or suppress ovulation. Such treatment usually leads to more copious secretion and appearance of actively motile sperms in the aspirated fluid, and occasionally to conception in a previously subfertile couple. Œstrogens have been used in an attempt to correct the abnormal cycle associated with menorrhagia, and render the patient more fertile, though it is doubtful whether they do so. For this purpose they are given in relatively high doses, such as 3 to 6 mgm. stilbœstrol daily, during the first twenty days of the cycle. Sometimes progesterone or ethisterone is added to the œstrogen during the last ten days of the course.

Indeed, there are only two effects of œstrogens which can be

almost always depended upon to yield therapeutic results in gynæcology. Œstrogens can stop uterine hæmorrhage and they can inhibit ovulation.

Œstrogen Hæmostasis. The hypothetical conception of the three levels of effective concentration of œstrogen in connection with uterine bleeding (Fig. 34) may help one to understand the

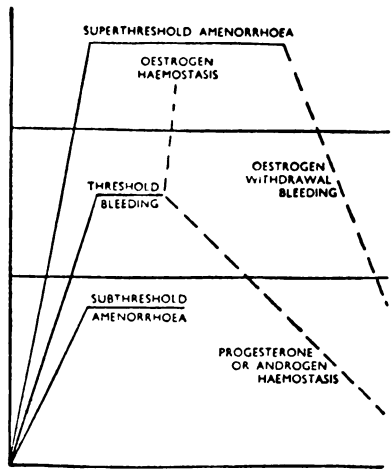

FIG. 34.

From " Gynæcological Endocrinology for the Practitioner " (E. & S. Livingstone Ltd.).

rationale of giving œstrogens to stop uterine bleeding though the actual mechanism is probably much more complicated and may, in fact, be entirely different. Sub-threshold levels fail to produce uterine bleeding : so do supra-threshold levels, though if the level drops, by discontinuing œstrogen therapy for instance, œstrogen withdrawal bleeding will take place. Whenever the level of effective concentration of œstrogen enters the bleeding threshold bleeding will take place. To stop this bleeding one must either raise or lower the effective concentration of œstrogen by giving more œstrogen on the one hand, or opposing its action with progesterone or androgen on the other. One may give œstrogen and produce bleeding : one may give more œstrogen and stop it. Thus, in cases of metropathia hæmorrhagica, where flooding is alarming and uterine bleeding has continued for weeks, one can usually arrest the flow by giving an intensive course of high doses of œstrogen, such as ethinylœstradiol 0·25 mgm. (equivalent to

5 mgm. of stilbœstrol) every two hours until the bleeding stops, which it should within twenty-four to thirty-six hours. Toxic effects are frequent and here the need for a highly potent and easily administered natural œstrogen, such as equine conjugated œstrogen or equilin, in doses of 10 to 15 mgm. two hourly, is indicated.

Inhibition of Ovulation. It is firmly established that spasmodic dysmenorrhœa is always associated with ovulatory cycles and is almost certainly due to the effect of progesterone on the uterine muscle. In order to prevent ovulation œstrogen must be given in doses of 2–3 mgm. of stilbœstrol (or its equivalent) commencing on the first to the fifth day of the cycle and continuing daily for fourteen days. This does not of course cure dysmenorrhœa, for even after months of such treatment successfully administered, dysmenorrhœa will return if the treatment is discontinued.

In Pregnancy. The work of the Smiths has brought the therapeutic use of the œstrogen in pregnancy into prominence. Briefly, they claim to have shown that in certain pregnancy disorders such as toxæmia and eclampsia there is deficient production of œstrogen and progesterone. They also claim that exogenous stilbœstrol alone or in combination with progesterone may correct the effects of this deficiency. Large doses are recommended, such as 5 mgm. daily at the 2nd month, increasing by 5 mgm. daily each week until by the 34th week 135 mgm. are being given daily. The claim that exogenous stilbœstrol increases pregnanediol output and therefore must stimulate endogenous progesterone secretion is disputed. Nevertheless this high dosage stilbœstrol therapy has been used in the treatment of threatened abortion and toxæmias and in diabetic mothers, and in the prophylaxis of repeated early miscarriages and eclampsia. It seems unlikely that administration of these high doses of stilbœstrol can be harmful during pregnancy though the principles and practice of the Smiths in the treatment of pregnancy disorders are by no means universally accepted, and the claims of Priscilla White to have improved the fœtal survival rate when diabetic mothers are treated with stilbœstrol and progesterone are critically discussed in the section on diabetes and pregnancy (see p. 106). It is now also generally agreed that œstrogen therapy in cases of missed abortion, uterine inertia and the induction of labour has proved very disappointing. In fact the pendulum is swinging back from enthusiasm to cautious appraisal of the therapeutic value of œstrogens in pregnancy.

Œstrogens and the Mammary Gland. The male breast is

very susceptible to œstrogen and gynæcomastia develops readily when œstrogen is administered, especially to adolescent and youthful males. It is not seen so universally in elderly men, treated for instance for cancer of the prostate. Excessive endogenous œstrogen due to deficiency of liver function, which leads to ineffective conjugation of œstrogen, may also cause gynæcomastia. It is, unfortunately, not so easy to induce breast development in women with small, though genetically normal, breasts and there is really no satisfactory preparation for local inunction in this condition. In women whose breasts have completely failed to develop as the result, for instance, of ovarian agenesis, reasonably satisfactory development can be achieved by intensive courses of œstrogen, such as implantation of two or three 100 mgm. pellets of stilbœstrol, and once some degree of development has been achieved it does not tend to regress. For tender and painful premenstrual breast swelling associated with generalized nodularity (" fibro-adenosis ") œstrogens are of course contraindicated and androgens are often symptomatically effective. Œstrogens inhibit lactation in mothers of still-born infants, or those who do not propose to breast-feed, provided they are given adequate doses, and there is no harm in giving 15 mgm. of stilbœstrol daily for two or three weeks, provided treatment is initiated immediately after delivery. Relief of breast engorgement subsequently in the puerperium is apt to be less effective. The treatment of persistent lactation is disappointing. Œstrogen in large doses, is theoretically indicated, but though it may seriously disturb menstrual rhythm and give rise to heavy metropathic bleedings, it only occasionally leads to cessation of milk secretion.

Œstrogens in certain Disorders of the Skin and Mucous Membranes. *Seborrhœa* seems to be an androgenic manifestation. It is on the seborrhœic skin that acne develops. There is no doubt that œstrogens can diminish this seborrhœic tendency, and produce a smooth, silky, dry skin—literally the " schoolgirl complexion." Acne will therefore temporarily disappear. One should, of course, be chary of giving large doses of œstrogens to youths with acne, for fear of permanent testicular damage. However, it is probable that the damage is not permanent and that regeneration of seminiferous tubules will occur. Fortnightly or three-weekly courses of 3 mgm. of stilbœstrol, commencing on the first day of a period, may often result in satisfactory relief of the adolescent acne in schoolgirls or maidens in their early twenties. At least a week's interval should be allowed to elapse between

successive courses. Each course should therefore commence within the first five days of the menstrual cycle.

Keratoderma. A condition of hyperkeratosis of the skin of the palms of the hands, and sometimes of the soles of the feet has been described by Haxthausen as occurring in women past the menopause. It is sometimes relieved by an intensive course of œstrogen.

Kraurosis and Senile Vaginitis. Senile atrophy of the vaginal mucosa with submucous petechial hæmorrhages is associated with an anœstrous vaginal smear and atrophy of the labia. There is often also an intense itching in the vulval region due to skin atrophy. This condition often responds to short intensive courses of œstrogen, such as stilbœstrol 5 mgm. daily for three weeks. (Here a " non-toxic " natural œstrogen such as equilin would be extremely valuable). Leukoplakia of the vulva is not relieved by œstrogens, which should therefore not be administered, though there is no evidence that they are likely to encourage the development of local malignant changes.

Bucco-vulval Ulceration. There is a curious condition in which small aphthous ulcers of the gums or buccal mucosa and sometimes vulval ulcers appear before, during, and immediately after a period. Later the lesions may be manifest more or less continuously. Usually they disappear during pregnancy. It is possible, therefore, that they may be due to lack of œstrogen. Certainly an intensive course of œstrogen, such as two or three 100 mgm. pellets of stilbœstrol with cyclical courses of progesterone to prevent metropathic flooding, relieves the condition in many cases.

Carcinoma of the Prostate and Breast. The role of œstrogens in the treatment of inoperable carcinoma of the prostate and breast is discussed in detail in the next chapter.